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Jonathan J. Carmouche,[1] J. Edward Puzas,[1] Xinping Zhang,[1]

Prarop Tiyapatanaputi,[1] Deborah A. Cory-Slechta,[2] Robert Gelein,[2]

Michael Zuscik,[1] Randy N. Rosier,[1] Brendan F. Boyce,[1]

Regis J. O'Keefe,[1] and Edward M. Schwarz,[1,3]

[1]The Center for Musculoskeletal Research, University of Rochester Medical Center and
[2]Department of Environmental Medicine, University of Rochester,
School of Medicine and Dentistry, Rochester, NY, USA

[3]To whom correspondence should be addressed:

Edward M. Schwarz, PhD
The Center for Musculoskeletal Research,
University of Rochester Medical Center
601 Elmwood Avenue, Box 665
Rochester, NY 14642, USA

Phone (585) 275-3063

Fax (585) 756-4721

Edward_Schwarz@URMC.Rochester.Edu

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Abbreviations

AA	Atomic absorption
ABH/OG	Alcian blue, hematoxylin, orange G and eosin stain
AP-1	Activator protein-1
BPb	Whole blood lead
CBLS	Childhood Blood Lead Surveilence
COX-2	Cyclooxygenase-2
M-CSF	Macrophage colony stimulating factor
μL	Microliter
MMP9	Matrix metaloproteinase-9
NFκB	Nuclear factor-kappa B
NHANES	National Health and Nutrition Examination Survey
Pb	Lead
PBS	Phosphate buffered saline
PGE2	prostaglandin E2
ppm	Parts per million
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide
RANKL	Receptor activator nuclear factor kappa B ligand
TGFβ	Transforming growth factor-β
TRAP	Tartrate resistant acid phosphatase

Outline

Abstract

Lead (Pb) exposure continues to be a significant public health problem. In addition to acute toxicity, Pb has an extremely long half-life in bone. Individuals with past exposure develop increased blood Pb levels during periods of high bone turnover or resorption. Pb is known to affect osteoblasts, osteoclasts and chondrocytes and has been associated with osteoporosis. However, its effects on skeletal repair have not been studied. We exposed C57/B6 mice to various concentrations of Pb-acetate in their drinking water to achieve environmentally relevant blood Pb levels, measured by atomic absorption. After exposure for 6 weeks, each mouse underwent closed tibia fracture. Radiographs were followed and histologic analysis was performed at 7, 14 and 21 days. In mice exposed to low Pb concentrations, fracture healing was characterized by 1) a delay in bridging cartilage formation, 2) decreased collagen type II and type X expression at 7 days, 3) a 5-fold increase in cartilage formation at day 14 associated with delayed maturation and calcification, and 4) a persistence of cartilage at day 21. Fibrous non-unions at 21 days were prevalent in mice receiving very high Pb exposures. Pb significantly inhibited *ex vivo* bone nodule formation, but had no effect on osteoclasts isolated from Pb exposed animals. No significant effects on osteoclast number or activity were observed. We conclude that Pb delays fracture healing at environmentally relevant doses and induces fibrous non-unions at higher doses by inhibiting the progression of endochondral ossification.